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EXHIBIT 2

Current Red Blood Cell Transfusion Practices

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The appropriate use of blood transfusions remains variable among health-care institutions and patient populations. Transfusion practices are discussed in this article in relation to medical practice guidelines and utilization review. Specific transfusion practices in the settings of intensive care, orthopedic surgery, and open heart surgery are reviewed. A new, promising approach to improving transfusion outcomes is the use of transfusion algorithms. Transfusion algorithms may prove especially useful if they incorporate point-of-care testing that is both physiologic and patient-specific for transfusion decisions. Transfusion algorithms are discussed and data presented for cardiac surgical adults
(KEYWORDS: transfusion practices, medical practice guidelines, transfusion algorithms)

Medical practice guidelines are being promoted as a means to improve medical care.[1] Guidelines for transfusion practices can contribute to improved care only if they change physician transfusion behavior. However, guidelines are unlikely to change behavior unless there are incentives for physicians to do so.[2] In the absence of incentives, there is widespread skepticism about the value of guidelines or recommendations from consensus conferences. One promising approach is to guide the decision-making process by coupling the use of algorithms for the transfusion of blood and blood components with readily-available clinical information obtained from point-of-care testing, rather than laboratory-based assays. An overview of current transfusion practices and their relation to guidelines and the process of utilization review is presented.

Guidelines and Utilization Review: Are They Effective?

A recent review concluded that transfusion audits can improve transfusion practices if they are performed in a timely manner and are combined with education of the individual ordering physician.[3] Plasma and platelet products are particularly amenable to this approach. Two studies using concurrent education or consultation reduced plasma usage by 46% and 77%, respectively.[4,5] In another study, using a retrospective audit, inappropriate plasma use was reduced from 53% to 22% of units transfused.[6] Similarly, use of platelet transfusions were reduced by 56% and 14% in two studies that used consultation[7] and au-

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dit,[8] respectively. Another study followed all requests for transfusions with a nonrequested consultation. The authors report a reduction in transfusion of platelets by 44%, and plasma and cryoprecipitate by 57%, but a reduction in erythrocytes of only 19% during a 4-year period.[9] Other studies cast doubt on whether utilization review is really an effective process. Hoeltge et al.[10] used a combination of indicators to evaluate transfusions on medical and surgical services, and concluded that only 4% of transfusions were unjustified. Renner and colleagues[11] found the percentage of unjustified transfusions to be 1.4% before and 0% after an educational intervention. The percentages of transfusions that failed initial screening were also extraordinarily low: only 0.5% and 3.2%, respectively, before and after the intervention. At our own institution in 1994, in which 23,002 erythrocyte units were transfused, 48 transfusion events underwent peer review by the transfusion committee and only 2 cases (or a rate of 1 in 10,000) were thought to be unjustified.

These extraordinarily low rates of "inappropriate" transfusions may be a consequence of several factors. First, erythrocyte transfusion audits in circumstances of hemorrhage are difficult, if not impossible, to evaluate. These settings would include the emergency room/trauma unit, the operating rooms, and the intensive care units. For this reason, our institutional process of utilization review excludes transfusions administered intraoperatively. Yet, studies of transfusion practices in orthopaedic surgery indicate that at least 25% of erythrocyte transfusions in this setting can be, in retrospect, identified to be inappropriate.[12] Second, the clinical indicators that define "appropriate" transfusion practice may be too generous. In the study that concluded that 96% of transfusions were "appropriate," a posttransfusion hemoglobin level of 11 gm% was used as a threshold to distinguish "appropriate" from "inappropriate."[10] Third, the medical chart audit has substantial limitations. Clearly documented information as to why the transfusion was administered is commonly unobtainable. We found that in orthopaedic surgical patients, only 68% of postoperative transfusion events on the day of surgery had chart documentation of blood loss and/or change in vital signs,[13] laboratory hematocrit levels of 33.5% ± 0.9% before transfusion, and 31.3 ± 0.5% after transfusion. In addition, the rationale for transfusion was recorded in only 16% of day-of-surgery transfusions and in only 27% of transfusions administered on postoperative days. At our own institution, 9 of 48 cases reviewed by the transfusion committee throughout 12 months were thought to have inadequate documentation for the reason for transfusion.

With these limitations, one alternative approach to retrospective chart audit for utilization review is the prospective use of transfusion algorithms, in which the decision process is coupled with information that serves as clinical indicators for transfusion. These algorithms could potentially have significant impact in the intensive care units and in the surgical setting. Therefore, current transfusion practices in these settings are reviewed.

□ Transfusion Practices in the Intensive Care Setting

A recent study of transfusion practices in the intensive care unit was performed in 4,875 consecutive patients admitted to 6 Canadian tertiary-level intensive care units.[14] Overall, 28% of the patients received erythrocyte transfusions. However, the number of transfusions per patient-day ranged from 0.82 to 1.08 among institutions, with a mean of 0.95 units/patient per day. The authors found the institutional effect on this variability to remain significant even after adjusting for age and APACHE II score. They found that the most frequent reasons for administering erythrocyte were acute bleeding (35%) and the augmentation of oxygen delivery (25%). This latter observation may explain why, in a recent study,[5] altering physicians' transfusion trigger based on hemoglobin levels did not affect the transfusion outcomes in an intensive care setting. In this study, transfusion guidelines based on hemoglobin levels (as low as 7.0 gm% for asymptomatic patients) could successfully alter blood ordering practices, but they were not able to reduce overall blood use.[15] The mean hemoglobin level at transfusion was decreased from 8.5 gm% to 8.1 gm%, but the proportion of patients transfused and the number of units trans-

fused (per patient, or patient-day) did not change. As noted in another study,[14] patients are more likely to receive blood transfusions that are triggered because of hemorrhage, ischemia, or issues related to oxygen delivery.

In a recent study of critically ill patients with sepsis, a set of physiologic goals to optimize oxygen delivery (>600 mL/min/m²), was evaluated in a series of interventions, including fluid boluses, administration of blood products, and the use of inotropes.[16] Whereas the intervention group had the same complications, number of days on ventilator and in intensive care, and hospital charges compared with a standard therapy group (oxygen delivery goal of 450–550 mL/min/m²), the patients who did achieve oxygen delivery in excess of 600 mL/min/m² (in both groups) had significantly less mortality (14%) compared with patients who could not maintain this high level of oxygen delivery (mortality of 56%). This study illustrates the paradigm that interventions, including blood products, that are keyed to patient-specific physiologic clinical indicators can result in better clinical outcomes.[17]

□Transfusion Practices in Orthopaedic Surgery

Estimates of total hip replacements (135,000), total knee replacements (110,000), and hemiarthroplasties of the hip (77,000) suggest that 5% of all erythrocyte units transfused in the United States in 1987 went to patients undergoing joint replacement (DRG 209) surgery.[18,19] An analysis of blood transfusions among 6,472 patients in 151 hospitals who underwent joint replacement surgery in 1986 (a year in which only 1.5% of erythrocyte transfused were autologous) was performed.[17] In this study, it was found that 46% and 68% of patients who underwent knee and hip replacement, respectively, received blood transfusions. The authors observed an influence of gender on transfusion outcomes. Male and female patients undergoing primary hip replacement were transfused in 60% and 73%, respectively, of cases; in primary knee replacement, males and females were transfused in 36% and 50% of cases.

The influence of gender on transfusion outcomes was noticed previously. Friedman and co-workers[20] found that women and men were discharged from surgical services with similar hematocrit levels, despite lower admission hematocrit levels in women; this was a result of increased blood transfusions to female surgical patients relative to their male counterparts. This phenomenon was studied further in a single institution study of 525 elective orthopaedic surgical patients,[12] in which female patients were found to be overtransfused when compared with male patients. Clinical indicators that ranged from "generous" to "strict" for transfusion inappropriateness were analyzed (Table 1). The excessive transfusion rates were seen especially in the 70% of patients who had predonated autologous blood: 50% of these autologous blood donors were transfused in excess of needs, according to an "intermediate" clinical indicator, compared with 24% of patients who had not predonated autologous blood.

The discharge hematocrit levels for orthopaedic patients at our institution during this era ranged from 30.8% to 33.7%,[21] further underscoring the likelihood that perisurgical anemia was being treated too aggressively with blood transfusion therapy. A multicenter study at six hospitals also found similarly high discharge hemoglobin levels, ranging from 10.7 gm% to 11.0 gm% for patients undergoing joint replacement surgery.[22] Therefore, whereas autologous blood donation practices substantially reduced the likelihood of receiving allogeneic blood during the latter 1980s from 41% to as low as 18% of orthopaedic patients,[23] on the basis of the above studies, a considerable percentage of elective surgical patients received blood transfusions in excess of their needs.[24,25] Some of these patients could be identified to be at risk for transfusion because of preexisting anemia. In one study,[26] 34 (21%) of 162 consecutively evaluated orthopaedic patients had preoperative hematocrit levels of less than 39%. Therefore, patient-specific factors can be identified as predeterminants of the need for transfusion.

In addition to patient-specific factors, however, institutional-dependent factors may be responsible for transfusion outcomes. In one report of transfusion outcomes in patients who did not predonate autologous blood, the erythrocyte units transfused for initial total hip replacement surgery was 1.7

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TABLE 1 ■ Blood Transfusions in Complex* Orthopaedic Surgery

Clinical Indicator	*Percent of Patients Transfused in Excess of Blood Needs*	*p Value*
"Generous" (O.K. if erythrocyte losses ≥ 10% of baseline)		
Men	13	<0.001
Women	25	
"Intermediate" (O.K. if erythrocyte losses ≥ 20% of baseline)		
Men	33	<0.001
Women	49	
"Strict" (O.K. if erythrocyte losses ≥ 30% of baseline)		
Men	52	<0.001
Women	66	

*Hip revision, bilateral knee, and bilateral hip procedures.

Adapted, with permission, from Goodnough LT, et al. Transfusion 1992;32:64.

± 2.9[24]; yet another institution from the same time period reported 2.3 ± 1.5 units for the same procedure.[22] More recently, 382 Medicare patients at 5 hospitals in Massachusetts who underwent orthopaedic surgery were audited for transfusion outcomes.[27] The authors found substantial variability in the availability of autologous blood, either as predeposit (range 58–88%) or as intraoperative salvage (range 0–75%). They concluded that blood transfusions were avoidable in 37% of autologous transfusion episodes and in 10% of allogeneic transfusion episodes. They also found that the mean transfusion hematocrit levels were significantly higher for autologous units compared with allogeneic units: 28.4% versus 25.7%, respectively.

In summary, there is much evidence to suggest that transfusion practices in orthopaedic surgery remain in evolution. Despite diminished use of allogeneic blood in this setting, there is need for a more standardized approach to the application of various technologies used in autologous blood procurement, as well as a more standardized approach to transfusion practices.

□ Transfusion Practices in Cardiac Surgery

The evolution of cardiac surgery has been accompanied by blood conservation interventions that combined blood salvage techniques[28] along with acceptance of postoperative normovolemic anemia. This resulted in a single institution report of allogeneic erythrocyte transfusions in as few as 10% of patients undergoing elective coronary artery bypass graft (CABG) surgery.[29] However, in a later study from the same institution, researchers reported allogeneic blood transfusions in 40% of patients, largely as a result of changing patient demographics such as increasing age and redoes.[30] Considerable variation in transfusion practice among institutions was identified. A multicenter audit of 18 institutions demonstrated a wide range in allogeneic erythrocyte transfusion requirements for patients undergoing simple, first-time CABG surgery.[31] This variability was confirmed in two subsequent studies.[32,33] Follow-up studies of transfusion outcomes in cardiac surgical patients indicate that a substantial number of blood components in patients are transfused inappropriately.[34]

Issues of blood safety in transfusion medicine renewed interest in blood conservation and alternatives to blood transfusion.[35] Practice guidelines were summarized by the National Institutes of Health consensus conferences on perioperative transfusion of erythrocytes.[36] Yet, as these guidelines have suggested hemoglobin thresholds as low as 70 g/L for transfusion in surgical patients, concern was raised over whether the pendulum has swung too far.[37] Hematocrit levels of 18% were described to be as well tolerated by patients as levels of 27% during cardiac bypass.[38] Yet, patients were reportedly at risk for perioperative ischemic injury

in the setting of postoperative hemodilution to hematocrit levels that range from 21% to 24%, with a delay in myocardial metabolic recovery.[39] Hemoglobin levels were suggested as clinical indicators for transfusion in patients undergoing a coronary bypass[40]:

1. Hemoglobin of 60 g/L for well-compensated chronically anemic patients; healthy (ASA Class I and some Class II) patients undergoing intentional hemodilution; and patients undergoing hypothermic cardiopulmonary bypass.
2. Hemoglobin of 80 g/L for most postoperative bypass patients except those with left ventricular hypertrophy, incomplete coronary revascularization, low cardiac output, poorly controlled tachycardia, or sustained fever.
3. Hemoglobin of 100 g/L for patients unlikely to increase cardiac output, patients with symptomatic cerebrovascular disease, and elderly (age > 65) patients.

Others emphasize that it is unlikely that any hemoglobin level can be universally applicable.[41] More physiologic indicators of the adequacy of oxygen delivery were proposed.[17] The routine placement of a thermodilution pulmonary artery catheter in patients undergoing CABG surgery enables regular assessment of mixed venous oxygen saturation (SVO_2), along with hemodynamic variables such as cardiac index, heart rate, and blood pressure. Mixed venous oxygen saturation is an indicator of the relative balance between the total body oxygen supply and demand. As a sensitive but nonspecific indicator, SVO_2 represents a weighted balance from all perfused vascular beds. When arterial oxygen saturation is adequate (> 0.90%), the SVO_2 inversely reflects the oxygen supply–demand balance. Mixed venous oxygen saturation provides continuous quantification of global oxygen extraction, in which a mixed venous oxygen tension greater than 40 mmHg (SVO_2 approximately 75%) is believed to indicate adequate tissue oxygenation in most clinical states, and mixed venous oxygen tension less than 20 torr (SVO_2 approximately 30%) suggests inadequate tissue oxygenation.[42] The understanding that hemoglobin is a poor clinical indicator of erythrocyte mass and tissue oxygen delivery[43] focused attention on the importance of more physiologic indicators for blood transfusion in this setting.

Therefore, in addition to clinical indicators for erythrocyte transfusion (tachycardia, hypotension, oliguria, etc), physiologic indicators that indicate clinically significant impairment in the balance of oxygen supply and demand are also important. When the hemoglobin level falls below "acceptable" values, these physiologic indicators indicate a potential benefit from transfusion. However, the precise "acceptable" hemoglobin concentration range is unknown. The National Institutes of Health consensus conference concluded that most patients with hemoglobin levels greater than 100 g/L do not require blood, whereas most patients with hemoglobin levels less than 70 g/L benefit from blood.[36] However, silent perioperative ischemia was identified as a significant clinical problem in noncardiac[44] as well as cardiac[45] surgical patients, emphasizing that the heart is an organ at risk with regard to tissue oxygenation. In a recent case report, researchers illustrated that in a surgical patient whose hematocrit level was 27%, silent myocardial ischemia was corrected with the transfusion of two erythrocyte units.[46] Nelson et al.[47] reported that in high-risk vascular surgery patients, a mean hematocrit level of less than 28% on the first postoperative day was associated with myocardial ischemia in 10 of 13 patients and a morbid cardiac event in 6 of these patients. Therefore, hemoglobin levels from 70 g/L to 100 g/L, a range in which physiologic indicators may identify patients who can benefit (or not benefit) from blood, need to be the most closely scrutinized.

In previous studies, researchers found that although the erythrocyte needs of these patients are substantial, a combination of conservative transfusion practice and blood conservation that could provide the equivalent of four blood units might avoid allogeneic blood exposure in as many as 75% of patients undergoing CABG surgery.[48] Because 80% of erythrocyte transfusions are received on the postoperative day and 90% by the end of postoperative day 1, the effectiveness of interventions focused on these 2 days would be effective. Patients were found to be transfused in excess of their needs if decisions to transfuse are made on a clinical indicator, such as estimated blood loss, that

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☐Transfusion Algorithms

Although the discharge hematocrit level is useful in a retrospective understanding of transfusion outcomes,[21] transfusion guidelines using concurrent clinical indicators are necessary if physician transfusion behavior is to be altered. We conducted studies to evaluate the impact of point-of-care testing,[49,50] in which intraoperative assays (on-site evaluation of whole blood prothrombin time, activated partial thromboplastin time, and platelet count, with results available within 4 minutes) were linked with a transfusion algorithm (Figure 1) for plasma and platelet transfusions in cardiac surgical patients.

This algorithm approach reduced blood component transfusions for the algorithm-treated patients group, compared with patients treated with standard practice using laboratory-based testing. Sixty-six patients with a diagnosis of microvascular bleeding were randomized to either standard therapy (n = 36), in which blood products were transfused at the discretion of the physician according to any laboratory-based test results requested; or to an algorithm group (n = 30), in which on-site platelet count, prothrombin time, and activated partial thromboplastin time results were available within 4 minutes. Platelet and plasma therapy were given according to an algorithm, according to on-site results.

The three decision pathways of this algorithm were based initially on platelet count measurements, followed by branch pathways determined by prothrombin time and activated partial thromboplastin time results. Both intraoperative and initial postoperative chest tube drainage were less in the algorithm group, indicating that hemostatic therapy was more successful in treating microvascular bleeding in the algorithm group. Point-of-care testing and patient-specific (i.e., targeted to each patient's laboratory test results) blood component therapy may have better distinguished hemostatic versus surgical bleeding for the surgical team at the close of the procedure, as suggested by the fact that only one patient in the algorithm group required later surgical reexploration, compared with five pa-

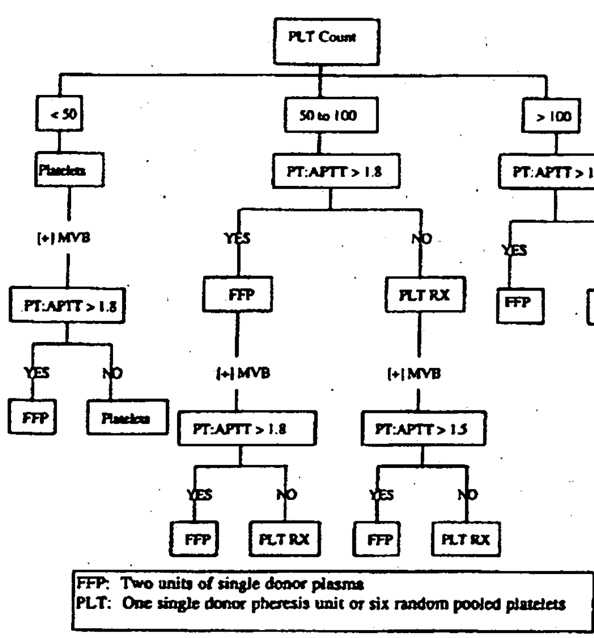

Figure 1. An algorithm approach for hemostatic therapy in cardiac patients determined to have microvascular bleeding after heparin neutralization. Platelets = platelet transfusion (6 units of random-donor or apheresis unit equivalent); PLT RX = platelet therapy (platelet transfusion and/or desmopressin acetate therapy at physician's discretion); FFP = plasma therapy (2 units of fresh-frozen plasma); [+] MVB = continued microvascular bleeding; PT:APTT = whole blood prothrombin time and activated partial thromboplastin time control values (values/mean values from a normal reference population); PLT count = platelet count (× 10³/mm³). Reprinted with permission from Despotis GJ, Grishaber JE, Goodnough LT. The effect of an inoperative treatment algorithm or physician transfusion behavior in cardiac surgery. Transfusion 1994; 34:290–296.

tients in the standard group. Eight (25%) of 36 standard therapy patients received different blood component therapy from what would have been designated by our algorithm.[50] The more effective therapy in the algorithm group was reflected in the lower erythrocyte transfusion needs in the algorithm group compared with the standard therapy group (5.9 ± 3.8 versus 9.8 ± 8.4 units, respectively). The improved patient care along with reduced blood transfusions resulted in substantial economic savings. This approach was described as a "powerful engine of change."[51]

Decisions to transfuse the surgical patient should acknowledge that patients are heterogeneous for risks related to anemia. One prospective approach to risk stratification for cardiac surgical patients has been published recently,[52] in which clinical variables determine whether a patient is considered as a "standard" or "increased" risk for cardiac surgery. Although complications related to anemia represent only one aspect of morbidity/mortality in this setting, the physiologic changes known to accompany acute anemia,[55] and the potential for myocardial tissue injury,[56] suggest that risk stratification for erythrocyte transfusion decisions would be prudent. A recent analysis of more than 2,000 cardiac bypass patients led to a model that calculated a transfusion risk score, which was then validated prospectively in more than 400 additional patients.[53] Now that cardiac surgery patients can be prospectively stratified not only for surgical risk but also for transfusion likelihood, the role of algorithms may be especially productive in the standardization of blood transfusion and blood conservation practices.

An algorithm that incorporates the balance between oxygen delivery and oxygen consumption as reflected by changes in SVO_2 within a range of hematocrit level, may be effective as a clinical indicator for erythrocyte therapy. Such an approach is illustrated in Figure 2.[54] With the recognition that transfusion support is dependent on both rate of blood loss and hemoglobin level, the decision to transfuse each unit of erythrocyte could be based on hemoglobin level, the quantity (rate) of blood lost, and hemodynamic parameters. Each patient would achieve adequate pulmonary capillary wedge pressures filling pressures with crystalloid/colloid therapy before entering a transfusion algorithm. Controlled clinical trials comparing this approach to current, unmonitored transfusion practices are needed.

If transfusion outcomes can be predicted from patient-related factors, then blood transfusion and blood conservation algorithms can be used to minimize the variability of transfusion outcomes related to institutional (procedural) and physician (transfusion practices)

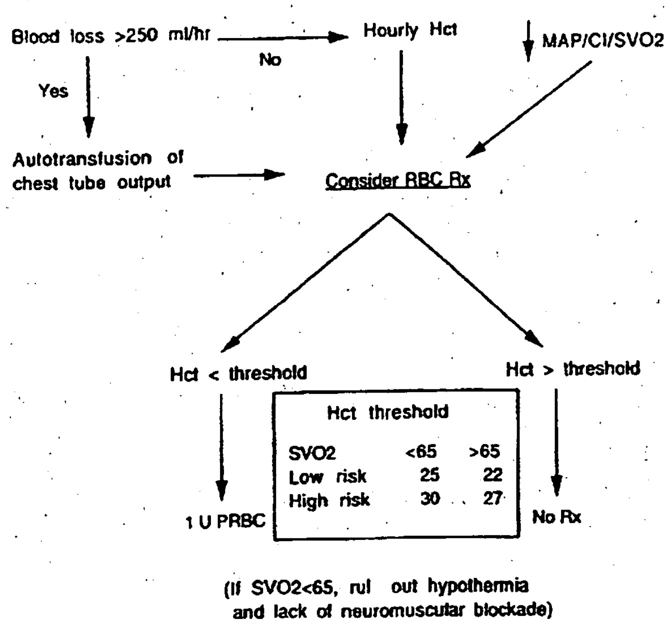

Figure 2. An algorithm approach for erythrocyte transfusion in cardiac surgical patients postoperatively. After establishing that the patient's volume status is adequate, decisions to transfuse would be based on hemoglobin/hematocrit level, rate of blood loss, and hemodynamic parameters. Thresholds for transfusion would differ for patients determined to be at "low" risk and "high" risk for perisurgical complications. Mixed venous oxygen percent saturation (SVO_2) could serve as a physiologic indicator of the balance between oxygen supply and demand for transfusion decision-making. Reprinted with permission from Goodnough LT, Despotis GJ, Hogue CW, Ferguson TB. On the need for improved transfusion indicators in cardiac surgery. Ann Thoracic Surg 1996;61:27–32.

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factors. Such algorithms could take into account patient heterogeneity by using the Higgins et al.[52] and McGovern et al.[53] stratification of "standard" and "increased" risk patients. Blood transfusions and blood conservation strategies could be administered according to algorithms incorporated into the daily practice of coronary revascularization.[51] Such an approach can then enable physicians to analyze transfusion outcomes, and the relation of these outcomes, to transfusion triggers, autologous blood procurement, pharmacologic interventions, and even emerging blood substitutes. The knowledge that we learn from the standardization of these practices, and the comparison of transfusion outcomes between different institutions or different therapeutic approaches, would form an important database that could serve as a reference for the continuous improvement of care in the surgical setting.[55]

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